

08/167,715

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### **Part III DETAILED ACTION**

1. Claims 4-6, 8 and 20-26 are being examined on the merits in this application. Claims 1-3, 7 and 9-19 have been cancelled.

2. The listing of claims as amended on page 10 of the amendment makes it easier to consider the issues at hand and is appreciated.

#### **OBJECTIONS/REJECTIONS WITHDRAWN**

3. The rejection of Claims 4-6, 8 and 20-26 under 35 U.S.C. § 112, second paragraph, as set forth in paragraph 2 of the last Office Action, is withdrawn in view of the instant amendments and applicants' arguments.

The rejection of Claims 20 and 21 under 35 U.S.C. § 102(a) as being anticipated by abstract no. 1632 of Morrissey et al. is withdrawn in view of the amendment to exclude the claims from encompassing the full length tissue factor.

The rejection of Claims 4, 6 and 20 under 35 U.S.C. § 102(b) as being anticipated by the January 1986 reference Guha et al. is withdrawn since Guha et al. apparently mistakenly obtained CD59, a distinct protein.

#### **OBJECTIONS/REJECTIONS MAINTAINED**

4. Applicant's arguments filed 11-17-94 have been fully considered but they are not deemed to be persuasive.

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

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5           The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10       6.     The objection to the specification and rejection of claims 22, 23 and 26 (now claims 20, 22, 23 and 26) under 35 U.S.C. § 112, first paragraph, as set forth in paragraph 4 and 5 of the last Office Action is **again made and maintained**. Claim 20, as amended, is also not supported by the original disclosure because the new subgenus of "from amino acid one to less than amino acid 263" was not originally described.

15           The specific grounds of Applicants' arguments against this rejection are not clear if present at all. Applicants' arguments against the 35 U.S.C. § 112, first paragraph rejection, in general are not persuasive because they do not address the issue of new matter and original written descriptive support for what is claimed. The specification did not explicitly or implicitly describe  
20     an encoded tissue factor protein having **both** the transmembrane and cytoplasmic region (and/or portions thereof) deleted. When one in this art speaks of the deletion of one or more amino acids or regions within a protein, the region of the protein C-terminal to the deletion does not simply fall off but is still part of the protein covalently joined where the amino  
25     acid(s) or region were deleted..

7.     The rejection of Claims 4-6, 8 and 21-26 (now claims 4-6, 8 and 20, 21, 23-25) under 35 U.S.C. § 112, first paragraph, as set forth in paragraph 6 of the last Office Action is **again made and maintained**. The

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specification is objected to and the claim 20 also rejected for the same reasons discussed regarding lack of broad enable for all deletions since claim 20 encompasses all deletion fragments and tissue factor protein down to one amino acid in length. Without guidance regarding which shorter fragments  
5 of the extracellular domain and the extent of fragmentation of the extracellular domain which can be tolerated it would require undue experimentation to determine such since one skilled in the art would not have the expectation of success in obtaining fragments, especially substantially smaller fragments.

10 Applicants argue in the next to the last paragraph of p. 5 of the instant amendment that the claims are limited to "human" tissue factor. However, this is incorrect. The only claims which might be said to be limited to human tissue factor are those which specify the sequence inherent to human tissue factor. As applicants note, in light of the instant specification, a  
15 limitation to specifically recite, human tissue factor, would be a merely limit the claims functionally to essentially a protein having activity in promoting coagulation in humans.

Applicants urge that they have shown a number of deletions can be made and activity retained since the entire transmembrane region can be  
20 deleted and tissue factor retains activity. However, this does not support the broad scope of all deletions but only provides the expectation of success in deleting the transmembrane region. Deletion of transmembrane regions was known in the art and would have been expected to work, particularly since such region was not the active portion of proteins having such a region which  
25 characterized the proteins activity. Deletions within the active portion (i.e., the extracellular domain), however, would have been unpredictable since the proteins function depends upon its structure which is made up of the sequence of amino acids in the protein and elimination of portions (e.g.,

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especially more than one to ten amino acids) within the active region without specific guidance would, accordingly, have had unpredictable effects and those skilled in the art would not have had the expectation of success in doing so at the time the invention was made. Applicants allege that a tissue factor as small as 209 amino acids has "subsequently" been reported to be active in a factor VII assay (i.e., apparently having tissue factor activity?). However, 209 amino acids is still 95% of the size of the 219 amino acid extracellular domain and, even if published before the priority filing date when the invention was made, would provide but little guidance to the skilled artisan regarding where other deletions could be made or the extent of such deletions which could be made in the extracellular domain or the minimal size of a tissue factor protein. While not particularly relevant, since it was "subsequent" to the filing date, production of a 209 amino acid length mutant does not show that undue experimentation was not required to do so.

Applicants cite publications published after the date of the invention which show the rather large divergence in amino acid sequence identity between the instant human tissue factor protein and those of bovine (70.4%), mouse (57.2%) and rabbit (74.1%). Of course, regarding any expectation of success in obtaining tissue factor protein from other animals, it is well settled that the publications teachings cannot support the instant disclosure since these were published after the date of the invention. Further, since the properties of the proteins having such divergence would likely have been different due to the presence of at least 25% different amino acids, it is unpredictable whether the same or obviously similar purification procedures could have produced them. Additionally, the mouse and rat DNAs (see the attached sequence alignments) would not hybridize to the human sequence even under low-stringency conditions since the DNA sequence identity with the human sequence is 62% and 61%, respectively, and Lathe teaches that

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anything below about 66% could not be distinguished from sequences hybridizing by mere chance alone even when long sequences were used (see col. 1 of p. 5 under "(c) Minimum homology for hybridization" and col. 2 of p. 10. The fact that these other mammalian genes have since been cloned  
5 does not show that undue experimentation was not required in obtaining them. Thus, even if, in arguendo, the homology data argued by applicants were known at the time the invention was made, other animal and mammalian tissue factor proteins in general might arguably be considered patentably distinct in view of their diversity and the expectations of a large  
10 number of false positives when screening DNA libraries with the disclosed sequence or with probes therefrom. Regardless, what must be considered was what was known at the time the invention was made. Applicants disclosed only one sequence from one organism and whether there was sufficient homology with any other organisms was unknown and those skilled  
15 in the art would not have had the expectation of success. The instant situation is similar to that in Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027, cited in the last Office Action, where it was held that it would have been merely obvious to try to get the human sequence given the  
20 sequence of the very closely related mammal, baboon, and knowledge of an overall homology of baboon DNA and human DNA of about 90% because neither the human EPO gene nor its exact degree of homology with the known baboon gene was known at the time the invention was made. The fact that the EPO genes from the two mammals were found to be virtually  
25 identical once the human gene had been cloned and sequenced was irrelevant to the determination made. The decision also closely relates to the issue of the various classes of analogs and functional analogs broadly encompassed by the claims wherein the court found that disclosure of only a few analogs did

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not broadly enable the functional analogs encompassed (see especially p. 1027 of 18 USPQ2d in the Amgen decision).

One of the main considerations to be made in determining whether undue experimentation is required is the **amount** of experimentation required (see Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986). If substitutions with the 20 natural amino acids encoded by DNA were the only modifications encompassed, even instant claim 6, limited to one to ten insertions, deletions or substitutions, would still broadly encompass well over  $4.3 \times 10^{28}$  substitution species (i.e., calculated as  $20^N * (\text{length})! \div N! \div (\text{length} - N)!$  wherein "20" is the number of natural amino acids encoded by DNA, "N" is the number of substitutions encompassed (i.e., in the instant case, 10), "!" is the factorial symbol and "length" is the total number of amino acids in the protein or peptide). The formula take into consideration not only the number of possible combinations of 10 amino acids (i.e.,  $20^{10}$ ) but also the fact that the substitutions can occur in any of "(length)" positions excluding the number of substitutions encompassed (i.e.,  $* (\text{length})! \div N! \div (\text{length} - N)!$ ). The figure of  $4.3 \times 10^{28}$  species is even far less than that encompassed by the claims since the total length of the mature protein is 263 amino acids but a maximum length of only 170 amino acids could be used in the above formula due to limitations of the Examiner's calculator. In putting these numbers in perspective, it is noted that the earth is estimated to have existed for  $10^{17}$  seconds (see p. 94, paragraph 1 of the 1983 reference of Creighton). Even if one species could be made and tested each and every second from now on it would require more than  $10^{20}$  years just to test a mere representative 10% of the encompassed species of claim 6 [i.e., calculated as  $(4.3 \times 10^{28} \div 10) \div (\text{the number of seconds in a year, i.e., } 60 \text{ seconds/minute} * 60 \text{ minutes/hour} * 24 \text{ hours/day} * 365 \text{ days/year})]$ . Thus, even if the various substitutions and modifications in tissue factor protein

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alleged to have been made in the art had been made at the time the invention was made, such would not provide guidance commensurate in scope with the claims.

As previously discussed, and as implicitly noted in the next to the last paragraph of p. 5 of the instant amendment, "tissue factor protein", when read in light of the specification, is a functional limitation and claim 4 is not limited to encompass only the types of substitutions of the Markush grouping, especially since dependent claim 6 also encompasses deletions and insertions not recited in claim 4. While claim 6 excludes prior art proteins not having the substitutions of the Markush grouping, claim 6 still broadly encompasses any other modification which can be made and the protein still be "tissue factor protein". Thus, dependent claim 25, for example, which is not limited to the sequence of Figure 2, while it excludes prior art tissues factors not having their potential proteolytic sites modified, also broadly encompasses any modification which can be made and the protein still be "tissue factor protein". This is not to say that the Markush grouping of substitutions of claim 4 would be commensurate in scope with the enablement of the specification if applied only to the sequence of Figure 2 since the substitutions of the Markush grouping are of a largely non-conservative nature and for the reasons previously discussed.

The objection/rejection with regard to the narrow issue of glycosylation is withdrawn since this specifically taught species has been shown to be workable.

8. Applicants remarks regarding the allowance of the divisional application and its' placement in an interference have been noted. However, the Examiner has not been able to determine the interference No. of the

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interference to which Applicants refer and none of the parent applications of the instant case nor any continuing cases corresponding thereto show the status of being allowed or in an interference. Additionally, since at least one claim should be allowable in the instant case before being joined to an interference and/or since prosecution in all the applications not in the interference having the same inventor or assignee should be carried out as far as possible and in view of the significant scope and new matter issues remaining in the instant application which should be resolved before a determination is made whether the claims are drawn to a divisible distinct invention and/or whether the claims dominate matter claimed in the application involved in the interference, or whether to join the instant application to the interference or to reject the instant claims over the count under 35 U.S.C. § 102(g) and suspend the application pending outcome of the interference, no determination with regard thereto is deemed appropriate at this time. See MPEP 2315.01.

9. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R.

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§ 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

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10. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1814.

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Papers relating to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 308-4227. Papers may be submitted Monday-Friday between 8:00 am and 4:45 pm (EST). Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Keith Furman whose telephone number is (703) 308-3453. The examiner can normally be reached on Monday-Thursday from 7:30 AM-5:00 PM. The examiner can also be reached on alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bob Wax, can be reached at (703) 308-4216.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

5 February 13, 1995

  
KEITH C. FURMAN, Ph.D.  
PRIMARY EXAMINER  
GROUP 1800

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